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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 000123woMegn	FOR FURTHER ACTION SeeNotificationofTransmittalofInternational Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/00390	International filing date (*day/month/year*) 19 January 2000 (19.01.00)	Priority date (*day/month/year*) 22 January 1999 (22.01.99)
International Patent Classification (IPC) or national classification and IPC C12N 9/64, C07K 16/40, A61K 38/48, 48/00, 39/395, G01N 33/53, C12Q 1/68, C12N 5/10		
Applicant MEMOREC MEDICAL MOLECULAR RESEARCH COLOGNE STOFFEL GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08 February 2000 (08.02.00)	14 May 2001 (14.05.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/00390

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-6, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages 1-13, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages 1-22 (SEQ ID NOs. 1-20), as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

The application discloses a plurality of polypeptide and polynucleotide sequences, which are alleged to have protease activity and to be involved in the pathogenesis of Alzheimer's and various other pathological conditions.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/00390

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

See separate sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: II.3

Priority

Sequence ID Nos. 2 and 10 could not be found in the 3 priority documents. Claims which have these sequences as subject matter cannot therefore claim a valid priority. Documents marked as "P" or "E" in the international search report form part of the prior art for these claims.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4,6-12 (partially), 5, 13.

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-4, 6-12 (partially), 5, 13 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As stated in the International Search Report, no opinion can be given on the novelty, inventive step or industrial applicability of polypeptide antagonists or inhibitors as defined in Claim 5 of the application. No opinion can therefore be given on the novelty, inventive step or industrial applicability of the corresponding parts of dependent **Claims 8-12**. The opinion on the aforementioned claims is restricted to drugs or diagnostic aids containing a protease as defined in Claims 1-3, a nucleic acid as defined in Claim 4 and/or an antibody as defined in Claim 6.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

See separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-4, 6-12 (partially).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3

Lack of unity of the invention

The IPEA agrees with the ISA regarding lack of unity (see Form PCT/ISA/206). There are accordingly 10 groups of inventions in the application as detailed below.

1. Claims: 1-4, 6-12 (part)

Protein with two aspartate radicals in a catalytically active structure, a first aspartate radical being in a motif X1GX2D and a second aspartate radical being in a motif X3X4DX5; X1, X2, X3 and X5 being selected independently of each other from the following: Ala, Val, Leu, Met and Ile; and X4 being an aromatic amino acid, and the motifs X1GX2D and X3X4DX5 being located in a transmembrane region; which protein has the sequence PAFX6YX7V, X6 and X7 being any amino acids, and the protein having the sequence SEQ ID No. 1; nucleic acid coding for such a protein and having the sequence SEQ ID No. 9; antibodies against the protein; methods of identifying inhibitors of the protein; drugs or diagnostic aids containing the protein, the nucleic acid or an antibody, and their use for the diagnosis or treatment of diseases whose cause is linked to the cleavage of amyloid precursor protein or to the impaired removal of hydrophobic signal peptides or to the accumulation of unfolded proteins in the endoplasmic reticulum; or to influence the presentation of hydrophobic peptides by histocompatibility complex molecules; a cell line not containing the protein of the invention or the corresponding nucleic acid.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3

2. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 10 and which contains the polypeptide sequence SEQ ID No. 2.

3. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 11 and which contains the polypeptide sequence SEQ ID No. 3.

4. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 12 and which contains the polypeptide sequence SEQ ID No. 4.

5. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 13 and which contains the polypeptide sequence SEQ ID No. 5.

6. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 14 and which contains the polypeptide sequence SEQ ID No. 6.

7. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 15 and which contains the polypeptide sequence SEQ ID No. 7.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3

8. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 16 and which contains the polypeptide sequence SEQ ID No. 8.

9. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 17 and which contains the polypeptide sequence SEQ ID No. 18.

10. Claims: 1-4, 6-12 (part)

As 1, but limited to a protein which is coded by the polynucleotide sequence SEQ ID No. 20 and which contains the polypeptide sequence SEQ ID No. 19.

The application does not meet the requirement of unity of invention (PCT Rule 13) for the following reasons.

The invention relates to the identification of proteins with two aspartate radicals in a catalytically active structure, a first aspartate radical being in a motif X1GX2GD and a second aspartate radical being in a motif X3X4DX5; X1, X2, X3 and X5 being selected independently of each other from the following: Ala, Val, Leu, Met and Ile; and X4 being an aromatic amino acid, and the motifs X1GX2GD and X3X4DX5 being located in a transmembrane region; which proteins have the sequence PAFX6YX7V, X6 and X7 being any amino acids. These proteins are said to have protease activity, although this has not been disclosed by the application. Polypeptides of this kind have already been described in the prior art.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3

For example, WO-98/40404 (page 24, line 5 to page 25, line 11) describes a human protein (human clone bk291_3) with the three aforementioned motifs (motif X1GX2GD between amino acids 220 and 224; motif X3X4DX5 between amino acids 176 and 179; and motif PAFX6YX7V between amino acids 276 and 282), the first two motifs being located in a region assumed to be a transmembrane region.

In the light of this prior art, the problem addressed by the present application can be described as being to provide additional proteins with two aspartate radicals in a catalytically active structure and with the sequence PAFX6YX7V. The sequences specified in inventions 1 to 10 correspond to different solutions of the aforementioned problem.

The identification of proteins with two aspartate radicals in a catalytically active structure and with the sequence PAFX6YX7V has already been described in the prior art; there is, furthermore, an essential difference between the individual polynucleotide and polypeptide sequences of the proteins of the different solutions. In the light of these facts and in the absence of further technical features which could be considered special technical features, the IPEA concludes that the ten inventions claimed in this application are not so linked as to form a single general inventive concept (PCT Rule 13.1).

There is therefore a lack of unity of invention. The

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3

contents of the different inventions which are not so linked as to form a single general inventive concept have been listed above.

Since the search report has been established only for the first four groups, only **Groups 1-4** are examined with regard to novelty, inventive step and industrial applicability in the international preliminary examination report.

The authority has chosen not to invite the applicant to pay additional fees for the examination of all four groups (PCT Rule 68.1).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4,6-12 (in part)	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-4,6-12 (in part)	NO
Industrial applicability (IA)	Claims	1-4,6-8 (in part)	YES
	Claims		NO

2. Citations and explanations

1 This report makes reference to the following documents:

D1: DATABASE GENEMBL [Online] 1 August 1998 (1998-08-01) LAMERDIN ET AL: 'FOS39554_1' XP002141740

D2: WO-A-98/40404 (GENETICS INST) 17 September 1998 (1998-09-17)

D3: WO-A-98/33916 (GENETICS INST) 6 August 1998 (1998-08-06)

D4: DATABASE GENEMBL [Online] 8 August 1996 (1996-08-08) HILLIER ET AL: 'zc51b02.r1 Soares senescent fibroblasts NbHSF Homo sapiens cDNA clone IMAGE:325803' XP002157596.

2 Novelty (PCT Article 33(1) and (2)):

2.1 None of the polypeptide or polynucleic acid sequences claimed is disclosed in its entirety in the prior art. The table overleaf summarizes the prior art. Documents D6(P), D7(P) and D8(P) correspond to WO-99/03990, WO-99/33873 and WO-00/17222, which are cited in the search report.

SIN*	Length	Document	Sequence	%ID**	Overlap
1 (aa)	592 aa	D1	O60365	98.7	203-592
		D5(P)	Y30715	100	1-320
		D5(P)	Y40022	100	321-592
9 (DNA)	1776 nt	-	-	-	-
2	520	D3	W75858 (SIN*17)	100	112-382
10	1560	D3	V54588 (SIN*16)	99.8	200-1560
3	377	D2	bk291_3	99.7	42-377
		D6(P)	Y01403 (SIN*103)	100	42-303
		D7(P)	SIN*16	100	1-377
11	1131	D2	bk291_3	99.9	77-1131
		D6(P)	HAQBI01 (SIN*31)	99.7	1-948
		D7(P)	OA004FG (SIN*18)	100	1-1131
4	384	D8(E)	SIN*128	100	1-384
12	1152	D4	A037159	99.6	610-1078
		D8(E)	SIN*35	99.9	1-1152

SIN = SEQ ID NO.** *%ID = % identity**

2.2 **Claims 1-4 and 6-12 (all in part)** are therefore acknowledged to be novel over the cited prior art.

3. Inventive step (PCT Article 33(1) and (3)):

3.1 The application claims to disclose proteases and their use in the treatment of various pathological conditions, without demonstrating that:

(a) the polypeptides defined actually have protease activity, or that

(b) they have any role in the diagnosis or treatment of Alzheimer's disease, in the presentation of hydrophobic peptides by the histocompatibility complex or in diseases with impaired signal peptide removal, or in accumulations of unfolded proteins.

Nor could any basis be found for the statement in the third paragraph of the description that the proteases are gamma-secretases, which are involved in the processing of APP. The IPEA has to be convinced that the stated problem is actually solved by the solution disclosed before it can acknowledge that an inventive step is involved.

3.2 In the present application there was nothing to suggest that the proteins disclosed fulfil the alleged functions. The present application cannot therefore be said to involve an inventive step. The provision of further putative proteins without the disclosure of any biological function is not considered inventive in relation to the prior art cited.

4. Industrial applicability (PCT Article 33(1) and (4)):

4.1 The PCT Contracting States do not have uniform criteria for assessing the industrial applicability

of Claims 9-12 in their present form. Patentability may depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 0017222	30 March 2000 (30.03.2000)	22 September 1999 (22.09.1999)	23 September 1998* (23.09.1998*)
WO 9903990	28 January 1999 (28.01.1999)	15 July 1998 (15.07.1998)	16 July 1997* (16.07.1997*)
WO 9933873	08 July 1999 (08.07.1999)	25 December 1998 (25.12.1998)	26 December 1997 (26.12.1997)
WO 0017222	30 March 2000 (30.03.2000)	22 September 1999 (22.09.1999)	23 September 1998* (23.09.1998*)

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI

* Documents marked with an asterisk have multiple priority dates.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Contrary to PCT Rule 5.1(a)(ii), the description does not cite D1-D4 or indicate the relevant prior art disclosed therein.